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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,229	10/06/2008	Peter Vollmers	50752/005001	1348

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
HALVORSON, MARK	
ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
12/07/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/586,229	VOLLMERS ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-10,13,14 and 58-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-10,13,14 and 58-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/17/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 2, 5-10, 13, 14 and 58-60 are pending and are currently under examination.

Objection to drawing withdrawn

The objection to Figure 16 is withdrawn in view of the submission of the new drawing.

Specification

Upon review it appears that the specification refers to SEQ ID NOs: 26 and 27 as being polypeptides and SEQ ID NOs: 28 and 29 are polynucleotides when in fact SEQ ID NOs: 26 and 27 are polynucleotides and SEQ ID NOs: 28 and 29 are polypeptides.

35 USC § 112 1st paragraph rejection maintained

The rejections of claims 1, 2, 5-10, 13 and 14 and new claims 58-60 for failing to comply with the enablement requirement are maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

As an initial matter, the specification is enabling for an isolated antibody comprising a heavy chain comprising CDR1, CDR2, and CDR3 regions comprising amino acids 28-32, 51-53, and 90-100 of the sequence of SEQ ID NO:29 and a light chain comprising CDR1, CDR2, and CDR3 regions comprising amino acids 11-18, 36-43, and 82-104 of the sequence of SEQ ID NO:28 respectively. The specification is not enabling for a polypeptide comprising amino acids 28-32, 51-53, and 90-100 of the sequence of SEQ ID NO:29 and a polypeptide comprising amino acids 11-18, 36-43, and 82-104 of the sequence of SEQ ID NO:28. The term “antibody” indicates a specific polypeptide that has two chains, a heavy chain and a light chain, whereby a polypeptide

does not necessarily comprise two chains. Furthermore, the specification is not enabling for an antibody that does not comprise all 3 CDRs from SEQ ID NO:28 and all 3 CDRs from SEQ ID NO:29. In addition, the term" fragment" has been interpreted as a polypeptide that does not comprise all 3 CDRs from SEQ ID NO:28 and all 3 CDRs from SEQ ID NO:29 in the correct orientation.

Furthermore, the specification while being enabling for a vector comprising the nucleic acid sequence of SEQ ID NO:26 and a vector comprising the nucleic acid sequence of SEQ ID NO:27 is not enabling for a vector comprising the nucleic acid sequence of SEQ ID NO:26 or a vector comprising the nucleic acid sequence of SEQ ID NO:27. Furthermore, the specification while being enabling for a nucleic acid encoding an antibody comprising a heavy chain comprising CDR1, CDR2, and CDR3 regions comprising amino acids 28-32, 51-53, and 90-100 of the sequence of SEQ ID NO:29 and a light chain comprising CDR1, CDR2, and CDR3 regions comprising amino acids 11-18, 36-43, and 82-104 of the sequence of SEQ ID NO:28 respectively is not enabling for an isolated nucleic acid molecule comprising nucleic acids 31-54, 106-129, and 244-312 of the sequence of SEQ ID NO:26, and 82-96, 151-159, and or 268-300 of the sequence of SEQ ID NO:27.

Thus, the rejections are more correctly classified as a scope of enablement rejections.

Applicants argue that the facts of the present case fall within the situation outlined in the Example of the submitted U.S.P.T.O. presentation and, therefore, the present claims should also be found to be enabled by the specification in view of the state of the art at the time of filing. Applicants argue that claim 1 and its dependent claims require the isolated polypeptide to include at least the sequence of amino acids 28-32, 51-53, and 90-100 of SEQ ID NO:29 (the 3 CDR sequences of the variable light chain). Applicants argue that claim 1 also requires the polypeptide to specifically bind to neoplastic cells or cells of a pre-cancerous lesion, but does not specifically bind to a normal cell. Applicants argue that claim 2 requires the polypeptide to further include amino acids 1 1-1 8,36-43, and 82-104 of SEQ ID NO:28 (the 3 CDR sequences of the

variable heavy chain). Applicants argue that the specification provides the sequence of the variable light and heavy chains of an antibody having the binding properties required by the claims. Applicants argue that, consistent with the analysis provided in the U.S.P.T.O presentation, the specification discloses an antibody with the claimed specific binding characteristics, the claims require the polypeptide to contain at least a fragment of the variable light chain or variable heavy chain having these binding characteristics, and as noted in the U.S.P.T.0 presentation, screening complementary variable domain libraries for antibodies that have the same binding characteristics was standard in the art at the time of filing.

Applicants argue that it would not require undue experimentation to make and use the polypeptides encompassed by claim 2. Applicants state that this claim requires the polypeptide to include the three CDR sequences of both the variable heavy and light chain sequences of the PAM- 1 antibody described in the specification. As such, the polypeptide of claim 2 contains all 6 CDRs of the PAM-1 antibody. Applicants note that the specification describes how to modify a polypeptide sequence to obtain variants that retain the binding specificity of the PAM-1 antibody

The U.S.P.T.O. example requires an antibody comprising a specified heavy chain that binds to a specific antigen or an antibody comprising a specified light chain that binds to a specific antigen. Applicants' claims are not drawn to an antibody as written in the U.S.P.T.O example. First, unlike an antibody, a polypeptide does not structurally require both a heavy chain and a light chain. Second, a polypeptide comprising 6 CDRs does not necessarily require that the CDRs are spacially orientated as in an antibody. A polypeptide comprising 3 CDRs encompasses a polypeptide in which the CDRs are adjacent to each other and not orientated as in an antibody. The U.S.P.T.O. example requires an antibody comprising a specified complete heavy chain that binds a specific antigen, an antibody comprising a specified complete light chain that binds a specific antigen or an antibody comprising the 3 CDRs from the heavy chain variable region and the 3 CDRs from the light chain variable region.

It would require undue experimentation to use an antibody comprising less than the the 3 CDRs from the heavy chain variable region and the 3 CDRs from the light

chain variable region. To comply with the enablement requirement the antibody must comprise the 3 light chain CDRs and the 3 heavy chain CDRs that bind a specific antigen. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce an antibody having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Given the structural importance of the framework residues of an antibody in correctly positioning the CDRs it would require undue experimentation to use an antibody that comprises only the 3 heavy chain CDRs or only the 3 light chain CDRs.

With respect to new claims 58-60, the term fragment is interpreted to mean an antibody fragment that does not comprise all 6 CDRs.

35 USC § 103(a) rejections maintained

The rejections of claims 1, 2, 5-10, 13 and 14 and new claims under 35 U.S.C. 103(a) as being unpatentable over Vollmers et al (Cancer, 1994, 74:1525-32, IDS) as evidenced by Brandlein (Human Antibodies, 2002, 107-119, IDS) in view of Robinson et al (U.S. Patent 5,618,920, filed 4/94).

The claims are drawn to an isolated polypeptide that specifically binds to a neoplastic cell or a cell of a pre-cancerous lesion, but does not specifically bind to a normal cell, wherein said isolated polypeptide comprises amino acids 28-32, 51-53, and 90-100 of the sequence of SEQ ID NO:29, wherein binding of said purified polypeptide results in the induction of apoptosis of the cell, wherein said proliferative disorder is tumors of the stomach, wherein said polypeptide is a functional fragment of an antibody selected from the group consisting of V.sub.L, V.sub.H, F.sub.V, F.sub.C, Fab, Fab', and F(ab').sub. The claims are also drawn to an isolated nucleic acid molecule comprising nucleic acids 31-54, 106-129, and 244-312 of the sequence of SEQ ID NO:26, and/or 82-96, 151-159, and or 268-300 of the sequence of SEQ ID NO:27 and a

vector comprising the nucleic acid sequence of SEQ ID NO:26, or SEQ ID NO:27.

Vollmers et al disclose an antibody 103/51 that binds to tumor antigens expressed on gastric adenomcarcinoma cell lines page 1528, Table 2). As evidenced by Brandlein, antibody 103/51 is Pam-1 (page 108, 1st column). The antibody, PAM-1 comprises SEQ ID NOs: 28 and 29. and is encoded by the nucleic acids of SEQ ID NOs:26 and 27. (Figs. 17, 18 of the present application)

Vollmers et al does not disclose an antibody comprising the sequence of SEQ ID NO:28 and SEQ ID NO:29 that is encoded by the nucleic acid sequence of SEQ ID NO:26, and SEQ ID NO:27.

Robinson et al teach the determination of nucleic acids encoding VH and VL of any known antibody and use of said VH and VL to produce recombinant antibodies (see column 1-45, and columns 12-22). Robinson et al teach that "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Robinson et al further disclose the use of Kabat to determine the variable region domains. (Example III). Robinson et al also disclose antibody fragments such as Fab fragments (column 5, lines 4-8).

One of ordinary skill in the art would have been motivated to apply Robinson et al's method determination of nucleic acids encoding VH and VL of an antibody to Vollmers et al PAM-1 antibody because Robinson et al states teach the determination of nucleic acids encoding VH and VL of any known antibody while Vollmers et al disclose that the antigen recognized by PAM-1 is present on gastric adencarcinomas. It would have been prima facie obvious to combine Vollmers et al PAM-1 antibody with Robinson et al's method determination of nucleic acids encoding VH and VL of an antibody to make nucleic acid molecules comprising SEQ ID NOs: 26 and 27 and an antibody comprising the amino acid sequences of SEQ ID NO:28 and 29.

Neither Vollmers et al nor Robinson et al disclose an antibody that induces apoptosis. However, the antibody of Vollmers et al and Robinson et al would inherently

induce apoptosis. The rejection based on inherency is based on the property that the PAM-1 antibody induces the apoptosis of tumor cells..

According to MPEP 2112

> "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Furthermore, as indicated in MPEP 2112

> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

The antibody of Vollmers et al and Robinson et al would inherently induce apoptosis of the gastric adenocarcinoma cell.

Applicants argue that neither Vollmers nor Brandlein, describes a PAM- 1 antibody that induces apoptosis. Applicants further argue that the PAM-1 antibody described in Vollmers and Brandlein induces proliferation of tumor cells. Applicants argue that the PAM- 1 antibody described by Vollmers does not inherently induce apoptosis of a tumor cell. Applicants argue that it was Applicants who discovered that a fragmented PAM- 1 antibody induces apoptosis. Applicants argue that cleavage of the pentameric PAM- 1 antibody into monomeric antibodies resulted in antibodies that induced apoptosis of stomach carcinoma cells *in vitro* and *in vivo* in a mouse model. Applicants argue that this property of a fragmented PAM- 1 antibody is not taught or suggested by the cited art, even if combined, and is reflected in the present claims which require that the binding of the polypeptide to the cell results in apoptosis of the cell. Applicants argue that the cited art fails to teach or suggest all of the elements

required by the claims and thus the cited art, even if combined, cannot render the presently claimed invention obvious.

Applicants' arguments have been considered but are not persuasive. The genetically engineered antibody of Vollmers et al, Robinson et al and Hellstrom et al comprise the sequences of SEQ ID NO:28 and SEQ IDNO:29. The finding that the pentameric antibody induces proliferation to tumor cells would have no relevance to the motivation for making the genetically engineered antibody of Vollmers et al, Robinson et al and Hellstrom et al. In response to applicant's argument that that it was Applicants who discovered that a fragmented PAM- 1 antibody induces apoptosis, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). The motivation for making the antibody of Vollmers et al, Robinson et al and Hellstrom et al would be that Vollmers et al disclose that PAM-1 binds to tumor antigens expressed on gastric adenomcarcinoma cell. Hellstrom et al teach that engineered antibodies may be conjugated with toxins to treat cancer. The engineered antibody of Vollmers et al, Robinson et al and Hellstrom et al would not be a pentameric antibody, as suggested by Applicants.

As previously stated, the binding of the engineered antibody of Vollmers et al, Robinson et al and Hellstrom et al would inherently induce apoptosis of the tumor cells. The specification discloses that binding of the antibody comprising the sequences of SEQ ID NO:28 and SEQ IDNO:29 induce apoptosis of tumor cells. (page 68, line 28 to page 69 line 2). The claims are drawn to an antibody comprising the sequence of SEQ ID NO:28 or SEQ IDNO:29 wherein binding of the purified antibody to the neoplastic cell results in the induction of apoptosis of the cell. Applicants have not convincingly demonstrated that the engineered antibody of Vollmers et al, Robinson et al and Hellstrom et al would not induce apoptosis upon the binding of the antibody to the tumor cell, as disclosed in the specification and claimed in the present application.

In response to Applicants arguments that while Vollmers (and Brandlein) describe the PAM- 1, these references fail to provide sufficient information for one skilled in the art to make and use this particular antibody, even if the disclosures were to be combined with Robinson, this rejection is based on the assumption that the antibody PAM-1 was publicly available to enable one of skill in the art to make a genetically engineered antibody comprising the sequences of SEQ ID NO:28 and SEQ IDNO:29. If the PAM-1 antibody was in the sole possession of the Applicants up to the filing date of the present application, an affidavit to that effect would obviate this rejection.

In response to Applicants argument that new claim 59 is free of the present obviousness rejection because it too requires the antibody to induce apoptosis of the neoplastic cell or cell of a pre-cancerous lesion to which it specifically binds, the claim is drawn to an antibody, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc.. Thus, the antibody of Vollmers et al and Robinson et al would inherently induce apoptosis of the gastric adenocarcinoma cell. As discussed above, the motivation for making a monomeric from the pentameric PAM-1 is that Vollmers et al disclose that PAM-1 binds to tumor antigens expressed on gastric adenomcarcinoma cell. Thus, the monomeric antibody can be used to detect gastric adenomcarcinoma cells or treat gastric cancer by conjugating the monomeric antibody with a toxin as described by Hellstrom et al.

Summary

Claims 1, 2, 5-10, 13, 14 and 58-60 stand rejected

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu, can be reached at (571) 272-0839. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark Halvorson
Patent Examiner
571-272-6539

/Misook Yu/
Supervisory Patent Examiner, Art Unit 1643